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CLINICAL PRACTICE

Portuguese recommendations for the use of biological and targeted synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis – 2020 update

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ABSTRACT

Objective: To update the recommendations for the treatment of rheumatoid arthritis (RA) with biological and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs), endorsed by the Portuguese Society of Rheumatology (SPR).

Methods: These treatment recommendations were formulated by Portuguese rheumatologists taking into account previous recommendations, new literature evidence and consensus opinion. At a national meeting, in a virtual format, three of the ten previous recommendations were re-addressed and discussed after a more focused literature review. A first draft of the updated recommendations was elaborated by a team of SPR rheumatologists from the SPR rheumatoid arthritis study group, GEAR. The resulting document circulated among all SPR rheumatologists for discussion and input. The level of agreement with each of all the recommendations was anonymously voted online by all SPR rheumatologists.

Results: These recommendations cover general aspects such as shared decision, treatment objectives, systematic assessment of disease activity and burden and its registry in Reuma.pt. Consensus was also achieved regarding specific aspects such as initiation of bDMARDs and tsDMARDs, assessment of treatment response, switching and definition of persistent remission.

Conclusion: These recommendations may be used for guidance of treatment with bDMARDs and tsDMARDs in patients with RA. As more evidence becomes available and more therapies are licensed, these recommendations will be updated.

Keywords: Targeted synthetic disease-modifying antirheumatic drugs; Guidelines; Rheumatoid arthritis; Biologics.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease, with an estimated prevalence of 0.7% in the adult Portuguese population[1]. The management of RA rests primarily on the use of disease-modifying anti-rheumatic drugs (DMARDs). These drugs reduce or reverse signs and symptoms, disability, impairment of quality of life, inability to work, and progression of

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joint damage and thus interfere with the entire disease process. DMARDs include biological agents (bDMARDs), conventional synthetic (csDMARDs) and targeted synthetic (tsDMARDs) chemical compounds[2].
The appropriate use of anti-rheumatic drugs is critical. It should be initiated as soon as the diagnosis is established, since its delay is associated with progressive joint damage accrual and lower likelihood of achieving a drug-free remission[3]. The treatment objective should be to reach remission at the earliest possible time point, based on a Treat-to-Target (T2T) strategy. T2T epitomizes the consensual concept that disease treatment should aim to achieve a target level of disease activity as early as possible and consistently maintain it[4, 5]. Clinical disease remission, or at least low disease activity, has become a possible and virtually mandatory target of treatment in recent treatment recommendations[2, 6].
Biological therapies with different mechanisms of action are currently approved for RA. In Portugal, five original tumour necrosis factor inhibitors (TNFi) (infliximab, adalimumab, etanercept, golimumab and certolizumab pegol), one interleukin (IL)-6 receptor (IL-6R) blocking monoclonal antibody (tocilizumab), a T cell stimulation inhibitor (abatacept) and one B cell depleting agent (rituximab) are available. Currently biosimilar (bs) of infliximab, adalimumab, etanercept and rituximab (bs-infliximab, bs-adalimumab, bs-etanercept and bs-rituximab, respectively) are also available. Other bs will soon enter the Portuguese market.
More recently, tsDMARDs were approved for RA treatment. They have overlapping mechanisms of action, despite having different selectivity and inhibition profiles[7-9]. Three Janus kinase inhibitors (JAKi) (baricitinib, tofacitinib and upadacitinib) are currently available in Portugal. Filgotinib, a JAKi already approved by the European Medicines Agency (EMA) for RA treatment, will soon enter the Portuguese market[10].
In 2003, the first version of the Portuguese Recommendations for the treatment of RA with biological therapy was developed by the Rheumatoid Arthritis Study Group (GEAR – Grupo de Estudos de Artrite Reumatóide) of the Portuguese Society of Rheumatology (SPR – Sociedade Portuguesa de Reumatologia) and published in Acta Reumatológica Portuguesa[11]. These guidelines have been regularly updated as new evidence is published and the experience of their use increases, with the latest recommendations published in 2016[12-16]. These recommendations are based on the standardized use of validated assessment tools of RA activity and impact: the disease activity score 28-joint count (DAS 28)[17], the Health Assessment Questionnaire (HAQ)[18] and the radiological assessment of Sharp score modified by van der Heijde (SvdH)[19]. A structured national registry of rheumatic patients (Reuma.pt), incorporating disease assessment tools for RA, has been created by the SPR and is available online[20].
This article presents the 2020 update of the Portuguese recommendations for the use of bDMARDs and tsDMARDs in RA. The review process focused primarily on the content of recommendations 6, 8 and 10. For its part, recommendations 1, 2, 3, 4, 5, 7 and 9 remained mostly unchanged compared to 2016. Although these recommendations contain some original concepts, their general structure follows the pattern of other international recommendations[2]. These recommendations were formulated by a team of SPR rheumatologists from the SPR rheumatoid arthritis study group, GEAR, based on literature evidence and consensus opinion. A national meeting was held, in virtual format, for presentation of new evidence, discussion and rephrasing of recommendations 6, 8 and 10, with the presence of forty-two SPR rheumatologists. A draft of the recommendations and supporting evidence was first circulated among all SPR rheumatologists for discussion and input. Finally, the level of agreement with each of all the recommendations was anonymously voted online by all SPR rheumatologists. Agreement was measured on a 10-point numerical rating scale (1=no agreement, 10=full agreement). These recommendations may be used for guidance in deciding which patients with RA should be treated with bDMARDs and tsDMARDs, how they should be monitored and which of them should be maintained on these therapies. The use of those therapies in RA is a rapidly evolving field and as more evidence becomes available and more therapies are licensed, these recommendations will be updated.

RECOMMENDATION 1
Rheumatologists are the specialists who should primarily care for RA patients. Treatment of RA patients with bDMARDs and tsDMARDs must be based on a shared decision between patient and rheumatologist.

The rheumatologist is the specialist who should treat and monitor patients with RA. There is current evidence that patients with RA followed up by rheumatologists, in comparison with other physicians, are diagnosed earlier, receive DMARD treatment earlier and have better outcomes in all major manifestations of RA[2, 21-27]. Nevertheless, since patients with RA have a high risk not only for disabilities related to their joint disease but also for comorbidities, such as infections, cardiovascular disease or malignancies, a multidisciplinary approach may be required in some cases.

Sharing medical decisions is the foundation of the partnership between physicians and patients. Shared decision is established between an individual Rheuma-

tologist and his Patient, as individuals, and should be considered a fundamental part of patient-doctor relationship and trust. It involves agreeing on the problem at hand, laying out the available options with their benefits and risks, eliciting the patient's views and preferences on these options, and agreeing on a course of action. Shared decision making not only increases patient and physician satisfaction with healthcare, but also may improve health outcomes[28, 29]. This recommendation focuses on the need for patient information regarding the risks and benefits of the treatment. Due to the complexity, high cost, and potential toxicity of therapies for RA, patient information is central to safety and quality of care.

RECOMMENDATION 2
Monitoring RA patients under treatment with bDMARDs and tsDMARDs is mandatory. These patients should be evaluated at closely spaced intervals, no longer than 3-4 months, to assess disease activity and safety issues. Function, quality of life and damage should also be evaluated during follow-up.

Follow-up should be provided at regular intervals, no longer than 3-4 months, for monitoring the efficacy of bDMARDs and tsDMARDs and identifying potential side effects. Tender and swollen joint counts, inflammatory markers [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)], patient global assessment of disease activity (PGA) and physician global assessment (PhGA) should be collected at each evaluation. Patients should be evaluated using composite activity indexes (Table I). The most commonly used index is the DAS28 ESR, which has validated cut-offs for different activity levels[14, 30]. Other composite measures using joint counts, with validated cut-offs for disease activity, can be used, such as the Simplified Disease Activity Index (SDAI)[31] or the Clinical Disease Activity Index (CDAI)[32]. The DAS28 CRP has no validated cut-offs for remission or low disease activity. All these variables and indexes are available in Reuma.pt. The global impact of the disease should also be evaluated. Assessment of functional impact using the HAQ, a validated tool available in Portuguese[33], should be performed when starting bDMARDs/ tsDMARDs and every six months thereafter. Physical Function not only provides information about the impact of RA but also predicts future outcomes. Quality of life (QoL) should also be regularly assessed. Generic tools, as the Medical Outcome Study Short Form 36-item (MOS-SF36)[34, 35] and the EuroQol five dimensions questionnaire (EQ5D)[36-38] are validated in Portuguese and available in Reuma.pt. Structural disease progression should be evaluated, on radiographs of hands and feet, when starting bDMARDs/ tsDMARDs and repeated thereafter to support future treatment decision.

Table I. Instruments to measure rheumatoid arthritis disease activity and to define remission (Adapted from [6])

Instrument	Thresholds of disease activity	
DAS28-ESR[25]	Remission	<2.6
	Low Activity	≥2.6 to <3.2
	Moderate Activity	≥3.2 to ≤5.1
	High Activity	>5.1
SDAI[26]	Remission	≤3.3
	Low Activity	>3.3 to ≤11
	Moderate Activity	>11 to ≤26
	High Activity	>26
CDAI[27]	Remission	≤2.8
	Low Activity	>2.8 to ≤10
	Moderate Activity	>10 to ≤22
	High Activity	>22

DAS 28-ESR: 28-joint Disease Activity Score Erythrocyte Sedimentation Rate; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index.

RECOMMENDATION 3
All RA patients receiving bDMARDs and tsDMARDs should be prospectively registered in the Reuma.pt.

Registries of patients with rheumatic diseases, especially under treatment with bDMARDs and tsDMARDs, allow monitoring of the treatment's efficacy and safety. These registries have contributed to the increasing knowledge on the performance of these drugs in the real world. All instruments required to monitoring RA patients are available in Reuma.pt[20].

RECOMMENDATION 4
The treatment target is remission or, at least, low disease activity.

Besides clinical benefit, remission status has a significant impact on progression of joint damage and deformities, physical function, QoL, comorbidities and mortality[39, 40]. Remission is considered as the absence of symptoms and signs of inflammation. The several available disease activity indexes define "remission status" differently (Table I)[30-32]. Observational studies have shown that remission definitions are only partially overlapping across the several indexes, being the DAS28-ESR the least stringent criteria[41-43]. In 2011, collaborative research of the American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) defined remission as having all the following measure-

ments below 1: tender joint count, swollen joint count, CRP and patient global assessment of disease activity[44]. These new criteria are associated with lower risk of radiographic progression and better outcomes[45, 46]. The proportion of patients reaching remission in clinical trials and clinical practice is sufficiently large to warrant its preferential use in clinical practice[2]. However, some studies have shown that many patients without clinical and laboratory findings of inflammation cannot be classified as being in remission due to the inclusion of PGA, making the ACR/EULAR remission difficult to apply in daily clinical practice, particularly in some clinical settings (eg. chronic pain syndrome, depression)[47]. In this context, PGA score might be in a large proportion due to other factors not related to inflammatory arthritis. In these difficult cases, more relevance can be given to the objective measures, like the inflammatory markers and swollen joints, since only those have been shown consistently to be associated with radiographic progression[48, 49]. In some cases, like patients with long-standing or destructive joint disease, in whom remission status is not achievable, low disease activity is acceptable[2].

RA patients report significant levels of disease impact, which are improved, but not fully abrogated by immunosuppressive therapy, even when remission is achieved. Therefore, there is a need for adjuvant interventions aimed at other uncontrolled domains of disease impact. This issue is detailed in the Portuguese multidisciplinary recommendations for non-pharmacological and non-surgical interventions in RA patients[50].

RECOMMENDATION 5
RA patients with inadequate response to methotrexate (MTX) at an optimal dose and for an adequate period of time, or to at least one other csDMARD or in case of contraindication or intolerance to MTX, should be considered for bDMARDs or tsDMARDs therapy.

MTX is the anchor treatment for RA patients, used in monotherapy or combined therapy, and should be part of RA's first-line treatment[2]. In case of contraindication or intolerance to MTX, leflunomide or sulfasalazine should be started. The optimal dosage of MTX is 25 mg/week for at least eight weeks[51]. The optimal dosage of leflunomide is 20 mg/day and of sulfasalazine is 3 g/day and may require a longer period to achieve optimal benefit[2, 52]. All patients with no clinical improvement after three months and all patients who fail to achieve at least low disease activity (DAS <3.2) at six months after starting csDMARD therapy should be considered as inadequate responders, and treatment should therefore be escalated to a bDMARD or a tsDMARD.

Short-term glucocorticoids should be considered as bridging therapy when initiating or changing csDMARD, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible[2].

RECOMMENDATION 6
If it is not possible to achieve the treatment target with an optimal csDMARD strategy or if there is contraindication/ intolerance to it, a bDMARD or a tsDMARD should be considered, preferably combined with a csDMARD. In patients who cannot use csDMARDs, IL-6 inhibitors or tsDMARDs should be considered.

Therapy with bDMARDs should be initiated with one of the following drugs authorized for first-line use: TNFi (infliximab, etanercept, adalimumab, golimumab, certolizumab pegol or approved respective bs) or tocilizumab. All the drugs mentioned above plus abatacept have been proven to effectively control disease activity, improve different patient-reported outcomes (PROs) and slow structural disease progression[53-79]. Unfortunately, in Portugal, abatacept is only reimbursed as second-line biological treatment, after failing to respond to at least one TNFi.

Indirect comparison between the different bDMARDs[80-82] and data from few head-to-head studies[74,75,83] did not show statistically significant differences in efficacy and safety between them. Since no factors are available for guiding drug selection, no preference for one over another agent is recommended. However, recent data from the nationwide Swedish register suggests that, as a first-line biologic treatment, non-TNFi (abatacept, rituximab and tocilizumab) showed better retention rate and efficacy (1-year EULAR Good Response/HAQ improvement) compared with TNFi, being tocilizumab the most efficacious and rituximab the drug with the longest retention[84]. These data are in line with findings from Reuma.pt, wherein treatment with tocilizumab in bDMARD-naïve patients was associated with better short-term effectiveness[85]. These results defy TNFi preference in daily practice[86], and require further validation with additional evidence. Moreover, a systematic review of the literature with the objective to provide an evidence-based decisional statement for the first-line biologic therapy in RA showed that the following preferences should be specially considered: abatacept in patients with high risk of infection; abatacept or tocilizumab in presence of latent tuberculosis infection and in patients with high rheumatoid factor and anti-citrullinated protein antibodies titers; etanercept in case of high cardiovascular risk[87]. Additionally, in a pooled analysis of sixteen observational RA reg-

istries, seropositivity for rheumatoid factor and/or anti-citrullinated protein antibodies was associated with increased effectiveness of rituximab and abatacept, but not TNFi[88].

Rituximab combined with MTX has proven efficacy in treating RA after TNFi failure[89-99] and is currently approved as second-line therapy. Pivotal trials for Rituximab approval were done in TNFi-naïve patients and showed its efficacy also in this context[100]. Moreover, rituximab has also been studied in patients with active RA that have not been previously exposed to MTX. In the IMAGE trial, rituximab plus MTX was effective in reducing signs and symptoms of the disease as well as preventing radiographic damage in MTX-naïve patients with early RA[101]. Another study also showed improvement of physical function and quality of life in a similar population[102]. Rituximab is not licensed for use as a first-line biological agent therapy. However, it can be used in first-line under specific conditions (see recommendation 7).

Therapy with tsDMARDs should be initiated with one of the following JAKis: tofacitinib (mainly JAK 1/3 inhibitor), baricitinib (JAK 1/2 inhibitor) or upadacitinib (selective JAK 1 inhibitor); all are approved by EMA and available in Portugal, in monotherapy or association with csDMARDs, for the treatment of moderate to severe RA in patients with inadequate response or intolerance to MTX.

In recent years, more data has emerged on the efficacy of JAKis: in the ORAL strategy trial, a double-blind, head-to-head, randomized, controlled trial, tofacitinib in combination with MTX demonstrated to be non-inferior to adalimumab in combination with MTX (difference 2% [98·34% CI –6 to 11])[103]; moreover, a double-blind, phase 3, placebo- and active-controlled trial showed that baricitinib in combination with MTX had better efficacy than adalimumab in combination with MTX[104]. Additionally, in a double-blind, phase 3, randomized, controlled trial, upadacitinib proved to be superior to placebo and adalimumab for improving signs, symptoms and physical function in RA patients who were receiving background MTX[105]. These latest results were confirmed at 48 weeks in the extension study[106]. Hence, in patients with RA irresponsive to csDMARDs, JAKi in combination with MTX demonstrated superiority or non-inferiority in comparison with adalimumab plus MTX.

In the absence of a head-to-head comparison of tofacitinib, baricitinib and upadacitinib, no preference of one over another can be advocated.

The most commonly reported side effects with JAKis are nausea, headache, iatrogenic dyslipidaemia, increased levels of transaminases and creatinine, changes in leukocyte and erythrocyte count, herpes zoster reactivations and respiratory/urinary infections[107-109]. Current evidence does not indicate an increased risk of malignancy with JAKis[110-113]. Available data suggests that there is no difference in the infection risk between JAKis and bDMARDs, except for the increased risk of herpes zoster infection with JAKis, which appear to be a class effect and more frequent in Asian populations[110, 111, 114, 115]. A recent systematic review and meta-analysis of randomized controlled trials assessed the cardiovascular risk of JAKis in RA, revealing no significant change in cardiovascular risk in a short-term perspective. However, more data are needed due to the reported increased risk of thromboembolism detected for both tofacitinib and baricitinib at higher doses[116]. Recently, data from the ORAL Surveillance, a post-marketing study including 4362 RA patients designed to compare the safety of tofacitinib versus TNFi with respect to major cardiovascular adverse events and malignancies (excluding non-melanoma skin cancers) showed that both primary endpoints (non-inferiority of tofacitinib compared to TNFi regarding major adverse cardiovascular events and malignancies) were not met. Moreover, there was no difference in those endpoints between the two doses of tofacitinib (5 mg twice daily and 10 mg twice daily)[117].

Based on the current evidence, bDMARDs and tsDMARDs should be preferably administered in combination with MTX. Several studies have established that a combination of bDMARDs with at least 10mg/week of MTX, increases the efficacy and retention rate of treatment[64, 100, 118-128].

Since the 2016 update, increasing evidence is also favoring the use of tsDMARD in combination with MTX. In the ORAL Strategy trial, tofacitinib monotherapy was not shown to be non-inferior to tofacitinib combined with MTX[103]. A post-hoc analysis showed that the efficacy outcomes were similar for tofacitinib monotherapy and tofacitinib plus MTX in early RA (≤ 2 years of disease duration) but were higher with the combination therapy than with tofacitinib monotherapy in established RA (>2 years)[129]. Nonetheless, real-world data from the US Corrona registry did not show significant differences in efficacy outcomes between tofacitinib monotherapy and tofacitinib combined with MTX[130]. In the RA-BEGIN phase 3 trial, baricitinib in combination with MTX conveyed significantly less radiographic progression than baricitinib monotherapy in an MTX-naïve population, although similar clinical and functional outcomes were noted[131]. However, no trials have compared baricitinib monotherapy with baricitinib combined with MTX in an MTX-inadequate response population.

In patients who cannot use concomitant therapy with csDMARDs, tocilizumab remains the only bD-

MARD with demonstrated consistent evidence of efficacy in monotherapy for symptomatic control and inhibition of radiographic progression[83, 130, 132-135]. However, in a recent analysis of the tocilizumab randomized trials, combination therapy with tocilizumab plus MTX proved to be more effective in preventing radiographic progression when compared to tocilizumab-monotherapy[136]. Still, in this study, the effectiveness of tocilizumab-monotherapy seems to approximate the effectiveness of the tocilizumab plus MTX in early RA patients with more joint damage and/or a lower DAS28 at baseline, and in established RA patients with longer disease duration[136]. Furthermore, a large observational study using data from the TOcilizumab Collaboration of European Registries in RA (TOCERRA) showed shorter drug retention under monotherapy, compared to combination therapy with csDMARDs, with an increasing difference over time after 1.5 years[137]. However, more recent data using the same registry showed that the risk of tocilizumab discontinuation was similar between monotherapy and combination therapy with csDMARDs in patients who had inadequate response to one or more bDMARDs[138]. Accordingly, in a multicentre cohort study using the Japanese ACTRA-RI registry, there was no difference in the duration of tocilizumab retention between monotherapy and combination therapy with MTX[139].

Although the results from ORAL Strategy and RA-BEGIN favored the combination therapy, they have also highlighted the potential efficacy of JAKis in monotherapy. Additionally, both tofacitinib and baricitinib as monotherapy have proven to be superior in efficacy compared to placebo[140-142] and to MTX alone[143-145]. Likewise, in the SELECT-EARLY trial, upadacitinib alone was superior to MTX in patients with predominantly early RA who were naïve for or had limited exposure to MTX[146].

If MTX is not tolerated or is contraindicated, IL-6R inhibitors and tsDMARDs should be considered preferential choices. TNFi approved in monotherapy can also be considered in case of patients with certain conditions: moderate hepatic impairment, high cardiovascular risk, high risk of blood clots and in women planning pregnancy (see recommendation 10).

Concerning bsDMARDs, the SPR position has been discussed in a separated article[147].

Of note, the cost-effectiveness of the drugs should also be taken into account in the treatment decision-making. The high prices of bDMARDs and tsDMARDs increases the direct costs of RA management and put pressure on the healthcare budgets. It is known that countries' socioeconomic status, affordability of bDMARDs and prescription and reimbursement rules influence the usage of these drugs[148]. On the other hand, the economic burden of RA includes not only direct costs (e.g. drug, inpatient and outpatient costs), but also indirect costs, such as those related to loss of productivity due to sick leave, reduced work performance and early retirement[149]. Indeed, the use of effective DMARDs can decrease both direct and indirect costs[150-153]. Overall, while efficacy and safety data should primarily underpin treatment decisions, cost issues should also be considered.

RECOMMENDATION 7

Rituximab can be considered as a first-line biological treatment in case of patients with other conditions: hematologic neoplasms [B-cell-lymphomas, acute lymphoblastic leukaemia or monoclonal gammopathy of undetermined significance (MGUS)], suspected latent tuberculosis in patients with contraindication to chemoprophylaxis, demyelinating diseases or specific manifestations of RA. The evidence of rituximab use in patients with recent solid neoplasms does not allow to state any recommendation; thus, a decision should be made case by case.

Rituximab has been used in patients with RA. However, the largest experience comes from its use in the treatment of some haematologic neoplasms like B-cell-lymphomas and acute lymphoblastic leukaemia. Based on this, it seems reasonable that in patients with active RA and current or recent history of these cancers, for whom other biological treatments and tsDMARDs are contra-indicated, rituximab could be used. There is no evidence to support the recommendation of rituximab use in case of recently cured neoplasms[154]. However, the absence of an increased risk of cancer in patients treated with rituximab supports the choice of some rheumatologists who prioritize rituximab in this setting[2, 155]. This measure should be carefully decided, based on individual risk-benefit and involving the oncology team. Cases of tuberculosis have not been identified in patients receiving rituximab[156]. Although rituximab therapy remains contra-indicated in active tuberculosis, its use can be considered in patients with suspected latent tuberculosis or living in endemic regions of tuberculosis who have contra-indication for chemoprophylaxis. bDMARDs are contra-indicated in patients with demyelinating diseases. Nevertheless, rituximab has been successfully used in patients with optic neuropathy and patients with other central nervous system demyelinating diseases, as multiple sclerosis, or with peripheral demyelinating neuropathies[157-160]. In patients suffering from both diseases (RA and demyelinating disease), rituximab could be considered.

RECOMMENDATION 8
Patients who failed a first bDMARD or tsDMARD should be treated with another bDMARD or tsDMARD. If the first bDMARD was a TNFi, the patient may receive a bDMARD with a different mode of action or a tsDMARD (swapping), or a second TNFi (cycling):
-A swapping strategy is recommended if the reason for discontinuation is a primary failure of a first TNFi or after two consecutive failures with TNFis;
-Following secondary failure or an adverse event to a first TNFi, cycling or swapping strategies are both acceptable.

The treatment goal of remission or low disease activity should be achieved after six months of therapy. However, the therapeutic response should be firstly assessed after three months on biological treatment or under a tsDMARD. It is expected to obtain at least a minimal clinical improvement (change in DAS28 >1.2 or change from high to moderate disease activity). In the absence of minimal clinical response at three months, it is unlikely that the treatment goal will be achieved even after one year of treatment[161], hence the treatment strategy should be redefined. Non-improvement at three months, or failing to achieve remission, or at least low disease activity, at six months should be considered a treatment failure.

Because of their long-term data on efficacy and safety, TNFis have been usually the first choice of biological therapy. Notwithstanding, approximately 30-40% of patients discontinue TNFis due to primary failure, secondary loss of response or intolerance[55, 162, 163].

Management of TNFi failure can include switching to an alternative TNFi (cycling) or to another class of targeted agents with a different mode of action (swapping)[164].

All bDMARDs and tsDMARDs proved efficacious in case of TNFi failure and are approved for this indication.

The cycling strategy is well established and supported by some RCTs (the OPPOSITE trial[165], the GO-AFTER[166, 167], the REALISTIC[168] and the EXXELERATE[169] study) and by several observational studies based on national registries or multicentric cohorts, which have highlighted a good efficacy profile and drug retention rate in RA patients receiving a second TNFi, comparing to placebo[170-179]. A recent meta-analysis including six RCTs and eighteen observational studies indicated that in TNF-experienced RA patients, subsequent TNFi therapy and subsequent non-TNF biologic therapy have comparable efficacy[180]. However, the overall performance of TNFi progressively decreases with the increasing number of previously failed agents.

Regarding the choice of the second TNFi, a multicentric, retrospective study based on an Italian cohort (LORHEN registry) that included 195 RA patients who switched from a first TNFi to etanercept, adalimumab, or golimumab, found that second-line golimumab has an overall better 2-year drug survival[181]. On the other hand, reasons for discontinuation of a first TNFi might influence the efficacy of a second TNFi. In fact, some studies, including a randomized trial, suggest that primary non-responders to TNFi are less likely to respond to a second TNFi than secondary non-responders to a TNFi or patients that discontinued the first TNFi following an adverse event[174, 175, 177, 182, 183].

On the other hand, the use of abatacept, rituximab, IL-6R inhibitors (tocilizumab), or JAK inhibitors (tofacitinib, baricitinib, upadacitinib) as a second-line agents (swapping strategy) is also strongly supported by RCTs (ATTAIN[184, 185]), REFLEX[91], RADIATE[186], ORAL STEP[187], RA-BEACON [188, 189], SELECT-BEYOND[190] and by real-life experiences[84, 92, 94, 97, 98, 191-204].

The best strategy after failure of a first TNFi has been intensely discussed in the last few years, and evidence is still conflicting when comparing the use of a second TNFi (cycling strategy) to a drug with a different mechanism of action (swapping strategy). The 2016 Portuguese recommendations[14] already pointed to the existence of data suggesting that patients with inadequate response to a TNFi who switched to a non-TNFi agent (tocilizumab, rituximab or abatacept) had significantly higher drug retention rates, compared to those that remain on TNFi treatment. Moreover, in the last few years, and due to the growing experience using these agents, new data on comparison of both strategies has emerged. A recent head-to-head, open-label RCT randomized 300 RA patients who failed a first TNFi to receive either a second TNFi or a non-TNFi biological agent (abatacept, rituximab, tocilizumab). The proportion of patients reaching a good or moderate EULAR response at week 24 (the primary endpoint) was higher in patients who received a non-TNFi biological agent, although the switching strategy was also often successful (69% VS 52%, OR, 2.06; 95%CI, 1.27-3.37; P = .004). There were no significant differences within the non-TNFi group[191]. Nevertheless, most data comparing the switching and swapping strategy comes from observational studies and national registries, with real-life observational data favoring the swapping strategy over the cycling strategy[84,92,94,97,98,192-204]). In Portugal, Santos-Faria *et al.* recently conducted a multicentric, non-interventional prospective study with 643 RA patients included in Reuma.pt registry who failed a first TNFi, showing higher drug retention rates (reflecting both effectiveness and safety) for rituximab and tocili-

zumab compared to a second TNFi, with similar persistence among tocilizumab and rituximab[199]. Even though there is more data regarding the use of abatacept, rituximab, and tocilizumab, some recent studies also included tofacitinib in this sort of analysis[196, 197]. Moreover, a 2016 meta-analysis including five RCTs that evaluated tofacitinib or bDMARDs against placebo after TNFi insufficient response demonstrated that tofacitinib 5 mg twice daily combined with MTX was found to have comparable ACR response and change from baseline in HAQ index with abatacept, golimumab, rituximab, and tocilizumab[205]. Concerning the choice between the non-TNFi drugs, there are conflicting data about which might be the best swapping option, not allowing for a specific recommendation, although the majority seem to favor rituximab or tocilizumab[92, 94, 98, 193, 202, 206].

With growing data on non-TNFi drug efficacy and safety, their use as first bDMARD is spreading. Hereupon, a new issue emerged on how to manage a non-TNFi failure. Some small exploratory studies[200,207,208] and a small RCT[209] showed that both TNFi and other non-TNFi are a suitable option after a non-TNFi failure, with higher retention rates in the swapping strategy[209]. To the best of our knowledge, studies on tsDMARDs failures are lacking. Due to the lack of good quality studies, no specific recommendation can be made regarding the best treatment strategy after failure of a first non-TNFi agent or JAKi as first-line targeted therapy, although increasing evidence suggests that changing the mechanism of action might lead to more efficacious results.

In summary all bDMARDs (TNFi and non-TNFi) and tsDMARDs have proved to be effective after the failure of a first TNFi. However, data from registries and observational studies appear to favor a change of the mechanism of action (for IL-6 inhibition, B cell depletion or T cell co-stimulation) as the best strategy for the treatment of these patients, with this being particularly true if the first TNFi is discontinued following inadequate response. JAK inhibition could also be considered but robust data comparing these agents with bDMARDs is missing. Due to lack of data, no specific recommendation could be made regarding the best treatment strategy after failure of a first non-TNFi agent or JAKi as first-line therapy.

RECOMMENDATION 9

In case of sustained remission, tapering bDMARDs or tsDMARDs can be considered, especially in patients with concomitant csDMARDs treatment. No specific recommendations about tapering regimens can be made at the moment.

Since 2011, several studies have demonstrated that bDMARDs can be tapered or even stopped without causing flares in a considerable percentage of patients[210-216]. In established RA, the available data suggest that many patients flare upon withdrawal of a TNFi, while those who tapered bDMARD more frequently maintain low disease activity and present less radiographic progression[215, 217, 218]. In the PRESERVE trial, patients assigned to receive etanercept at a lower dose (25 mg/wk) continued to have low disease activity in the double-blind period whereas those who received placebo (maintenance of csDMARDs only) had a mean disease activity in the moderate range. The groups given etanercept (50mg/wk or 25mg/wk) kept similar patterns of response and maintained a better efficacy than the group given placebo[217]. Similar findings were obtained in other studies[218, 219].

Contradictory results were observed in early arthritis. In the PRIZE trial, after attainment of sustained remission in early RA, dose reduction of etanercept, but not the withdrawal of the biologic, was accompanied by maintenance of response, with 63.5% of patients remaining in remission (DAS28 <2.6 at week 76 and 91 visits)[216]. Likewise, in the open label extensions of OPTIMA[220] and HIT HARD[211] studies, patients under bDMARD and MTX who withdraw the biologic agent, maintained good clinical[211, 220], radiographic[211, 220] and functional response[220] .

Even though most studies on dose reduction or withdrawal have been performed with TNFis, data on other bDMARDs (abatacept and tocilizumab) are emerging with similar overall results. However, the percentage of patients in remission at the end of the withdrawal studies has been small, ranging from 9 to 44%[73, 128, 134, 221-223]. Only one observational cohort study[224] evaluated dose reduction of tocilizumab, yielding at the end of the 24-week study, 55% of patients in low disease activity. In early arthritis, a more profound and persistent response increases the likelihood of maintaining a good outcome after withdrawal of a bDMARD, maintaining therapy with csDMARDs[225]. Gradual bDMARD dose reduction may be a better strategy than abrupt discontinuation[216-219, 226]. In case of relapse, reintroduction of the bDMARD appears to allow the return to a favorable outcome[221, 225, 227, 228].

Among tsDMARDs, the evidence on dose reduction is even scarcer. The RA-BEYOND study randomized patients from four trials on baricitinib at 4 mg who had achieved stable CDAI ≤10 to either continue 4 mg or reduce the dose to 2 mg. While more patients who continued full dose maintained CDAI low disease activity compared with those who reduced the dose (93% vs 83%, p<0.001 at three months; 87% vs 75%, p<0.001, at six months; 80% vs 67%, p<0.01 at 12 months for baricitinib 4 mg continuation vs dose reduction to

baricitinib 2 mg, respectively), a majority of patients maintained their good disease state despite dose reduction. Further, in patients being in CDAI ≤2.8 at randomization, fewer patients worsen their disease activity state. Of those who flared after dose reduction, most (66.7%) regained their CDAI <10 state within 24 weeks after a dose increase to 4 mg. Thirteen of the 16 patients who did not regain their CDAI <10 state after 24 weeks were able to do so at a subsequent time point[229].

Importantly, before bDMARDs or tsDMARDs tapering, glucocorticoids should be withdrawn[2].

RECOMMENDATION 10
In case of pregnancy, and always based on a shared decision between patient and physicians (rheumatologist and obstetrician), patients may be treated with most TNFi in its early stages. Certolizumab can be used throughout pregnancy.
The use of TNFi is appropriate during breastfeeding.
tsDMARDs and some bDMARDs (rituximab, abatacept and tocilizumab) should be avoided in pregnant and breastfeeding women.
There is no indication to stop bDMARD in males who wish to become parents.

TNFis are the best-studied biologic agents during pregnancy and safety data on TNFis during pregnancy is reassuring. The benefits of TNFis in controlling disease and achieving remission seem at current knowledge to outweigh the theoretical risk of fetus exposition to the drug. The decision should be shared between the patient and physicians (rheumatologist and obstetrician), balancing risks and benefits. TNFis differ in structure: adalimumab, infliximab, and golimumab are whole monoclonal IgG1 antibodies, etanercept only contains a part of the Fc-region of IgG1 and certolizumab is a PEGylated fragment antigen-binding (Fab) and contains no Fc region[230, 231]. Active transport of TNFis over the placenta into the fetal circulation is mediated through binding to the fetal Fc receptor and occurs as early as week 18 of gestation. Adalimumab and infliximab have a high affinity for the fetal Fc receptor; etanercept binds weakly to this receptor; certolizumab does not bind to this receptor at all since it does not contain an Fc-region. Hence, the level of TNFi that can be detected in the cord blood is associated with the type of TNFi[230, 231]. In addition, placental transfer increases over time and therefore the timing of administration during pregnancy is associated with the level of TNFi that can be detected in the cord blood. The lowest levels of anti-TNF in the cord blood are observed for certolizumab and etanercept. Exposure to infliximab and adalimumab, especially later in pregnancy, results in higher levels of the drug detectable in the umbilical cord blood compared to etanercept and certolizumab. Both infliximab and adalimumab can be detected in the infant serum up to one year for infliximab and up to 9 months for adalimumab[231, 232]. The best timing to stop anti-TNF treatment so that no levels of TNFis in the umbilical cord can be detected is yet to be determined. So, in line with the EULAR recommendations, we advocate stopping infliximab and adalimumab treatment at 20 weeks of gestation and etanercept at 30-32 weeks of pregnancy; we also advise that the use of certolizumab throughout the whole pregnancy is safe[230, 231]. Due to a lack of safety data, the use of golimumab is not advised during pregnancy[230, 231]. When taking all data together, no increased risk of congenital malformations in infants exposed to TNFis was found, and most importantly, no specific pattern of malformations could be observed[231, 233]. In addition, other authors showed, in a large study, no excess risk of serious infections after in utero exposure to a TNFi[231, 234]. However, we can say that the use of biologics in pregnancy is still controversial because safety for the fetus and neonate has been proven only for TNFis. Moreover, long-term outcomes for exposed children have not been studied for any biologic. Thus, extended long-term studies are needed to clarify whether biologics may affect immune function in prenatally exposed children. Safety data on other biologic agents (tocilizumab, abatacept and rituximab) and tsDMARDs is insufficient and the use of these agents is not advised during pregnancy[230, 231]. They are, therefore, best discontinued before a planned pregnancy, respecting the washout period between drug discontinuation and pregnancy, which vary according to the drug.

The JAK-STAT pathway has been shown to be involved in cell-cell adhesion and in cell polarity, which could condition the earlier stages of embryogenesis[235]. In rats, at a dose 73 times, but not 29 times, the therapeutic dose of 10mg twice daily, tofacitinib was teratogenic and caused fetal death[236]. Similarly in rabbits, at a dose 6.3 times, but not 1.5 times, the therapeutic dose of 10mg twice daily, teratogenic effects and post-implantation loss were verified[236]. Tofacitinib had no impact on male fertility or sperm quality or motility in animal studies[236]. In murine models, baricitinib, at doses higher than 20-times the human labelled dose, has shown to reduce fertility, to have a teratogenic effect, reduce bone growth and fetal weight in uterus and increase embryo death[235]. However, in humans, exposure to tofacitinib during conception and pregnancy in rheumatic diseases or ulcerative colitis seems not to be associated with increased risk to the fetus[237-239]. Moreover, a recent report of exposure to baricitinib during the first 17 weeks of pregnancy, outside the drug regis-

Table II. Recommendations for the use of biological therapies and tsDMARDs in rheumatoid arthritis

Domain	Recommendation	Agreement mean (SD)
General recommendation*	Rheumatologists are the specialists who should primarily care for RA patients. Treatment of RA patients with bDMARDs and tsDMARDs must be based on a shared decision between patient and rheumatologist.	9.9 (0.4)
	All RA patients receiving bDMARDs and tsDMARDs should be prospectively registered in the Reuma.pt.	9.0 (1.6)
Monitoring*	Monitoring RA patients under treatment with bDMARDs and tsDMARDs is mandatory. These patients should be evaluated at closely spaced intervals, no longer than 3-4 months, to assess disease activity and safety issues. Function, quality of life and damage should also be evaluated during follow-up.	9.2 (1.1)
Treatment target*	The treatment target is remission or, at least, low disease activity.	9.7 (0.7)
Treatment indication*	RA patients with inadequate response to MTX at an optimal dose and for an adequate period of time, or to at least one other csDMARD or in case of contraindication or intolerance to MTX, should be considered for bDMARDs or tsDMARDs therapy.	9.3 (1.3)
First-line treatment	If it is not possible to achieve the treatment target with an optimal csDMARD strategy or if there is contraindication/intolerance to it, a bDMARD or a tsDMARD should be considered, preferably combined with a csDMARD. In patients who cannot use csDMARDs, IL-6 inhibitors or tsDMARDs should be considered.	9.2 (1.0)
Specific comorbidities*	Rituximab can be considered as a first-line biological treatment in case of patients with other conditions: hematologic neoplasms [B-cell-lymphomas, acute lymphoblastic leukaemia or MGUS], suspected latent tuberculosis in patients with contraindication to chemoprophylaxis, demyelinating diseases or specific manifestations of RA. The evidence of rituximab use in patients with recent solid neoplasms does not allow to state any recommendation; thus, a decision should be made case by case.	9.2 (0.9)
Inadequate response	Patients who failed a first bDMARD or tsDMARD should be treated with another bDMARD or tsDMARD. If the first bDMARD was a TNFi, the patient may receive a bDMARD with a different mode of action or a tsDMARD (swapping), or a second TNFi (cycling): -A swapping strategy is recommended if the reason for discontinuation is a primary failure of a first TNFi or after two consecutive failures with TNFis; -Following secondary failure or an adverse event to a first TNFi, cycling or swapping strategies are both acceptable.	9.4 (0.7)
Sustained remission*	In case of sustained remission, tapering bDMARDs or tsDMARDs can be considered, especially in patients with concomitant csDMARDs treatment. No specific recommendations about tapering regimens can be made at the moment.	9.2 (1.1)
Pregnancy and breastfeeding	In case of pregnancy, and always based on a shared decision between patient and physicians (rheumatologist and obstetrician), patients may be treated with most TNFi in its early stages. Certolizumab can be used throughout pregnancy. The use of TNFi is appropriate during breastfeeding. tsDMARDs and some bDMARDs (rituximab, abatacept and tocilizumab) should be avoided in pregnant and breastfeeding women.	9.3 (1.0)
	There is no indication to stop bDMARD in males who wish to become parents.	9.4 (0.8)

Agreement was voted on a scale 1 to 10 (fully disagreement to fully agreement) by 102 Rheumatologists. *These recommendations remained mostly unchanged compared to 2016. bDMARDs, biologic disease-modifying anti-rheumatic Drugs. csDMARDs, conventional synthetic disease-modifying antirheumatic drugs. MGUS, monoclonal gammopathy undetermined significance. MTX, methotrexate. RA, Rheumatoid Arthritis. TNFi, Tumor Necrosis Factor inhibitor. tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs.

tration program, has been published and no teratogenicity was found[235].

There is only limited data available on the effect of stopping TNFi treatment on disease course in pregnant patients. Most literature suggests that stopping TNFis just before or during pregnancy may result in a flare during pregnancy or in the peri- and the postpartum period. Contrary, other authors showed that in patients with inactive disease, discontinuing TNFis before the 20th week of gestation did not result in active disease later in pregnancy[231, 240].

Infants who have been exposed in the second or third trimester of pregnancy to a TNFi should not receive live-attenuated vaccines (like varicella, measles,

mumps, rubella, rotavirus, intranasal influenza and BCG) in their first six months of life[230, 231]. Infants exposed to a TNFi before the 22nd week of gestation can get vaccinated, including with live vaccines, according to standard vaccine protocols[230, 231]. Vaccination appears to be effective in infants previously exposed to TNFis in utero.

Breastfeeding during the use of TNFis (infliximab, adalimumab, etanercept, golimumab and certolizumab) is appropriate since minimal transfer of the TNFi into breast milk occurs[230, 231]. tsDMARDs and bDMARDs with no data on breast feeding (rituximab, tocilizumab and abatacept) should be avoided during lactation[230].

Birth outcomes in children fathered by men treated with biologics before conception have been studied for TNFis[241]; for other biologics, data are anecdotal and of poor quality[242].Those studies did not show any negative impact regarding live births or congenital abnormalities[243, 244]. In men planning to conceive, due to a lack of safety data, JAKis should be discontinued.

GENERAL SAFETY CONSIDERATIONS

bDMARD and tsDMARD therapies are contra indicated in the following situations:

1) active infection (including opportunistic infections, active tuberculosis; human immunodeficiency virus, hepatitis C virus and hepatitis B virus infections)
2) Malignancy:
– Current or recent history of cancer (≤5 years), except basal and squamous cell skin cancer after complete excision
– No recommendations are possible at this moment regarding pre-malignant conditions
– In some cases, Rituximab can be considered (see recommendation 7). The use of other non-TNFis agents can be considered in individual cases based on benefit/risk assessment.
3) Concurrent administration of live vaccines
4) Heart Failure (New York Heart Association Class III or IV), in case of rituximab and TNFi
5) Demyelinating disease, except rituximab that can be used in some situations

Tuberculosis screening before introduction of tsDMARDS and biological therapies

Evaluation for latent and active tuberculosis should be performed in all patients with joint inflammatory diseases before starting bDMARDs in accordance with the recommendations developed by SPR and the Portuguese Society of Pneumology[245]. By extrapolation and general consensus, the same assessment should be performed before starting treatment with a tsDMARD.

Criteria for temporary suspension/ postponement of introduction of biological therapies

This issue is detailed in the practical guide for prescribing biological therapies published by SPR[246].

CONCLUSION

bDMARDs and, more recently, tsDMARds reflect an advance in the approach of RA patients. Its use plays an important role in RA treatment, leading to better outcomes. These updated recommendations reflect the new evidence on efficacy and safety published since 2016. The use of bDMARDs and tsDMARDs should be monitored regularly, regarding clinical efficacy and safety. Remission or at least low disease activity should be the treatment target. Precautions related to adverse events and contra-indications should be considered when these drugs are used. New drugs are being developed [other JAKis and IL-6 antagonists and drugs with new mechanisms of action]; thus, these recommendations should be updated when new evidence becomes available.

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